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Adverse events of glucocorticoids during treatment of rheumatoid arthritis: lessons from cohort and registry studies

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Abstract

Glucocorticoids have now been used for >65 years in the treatment of RA. There is good evidence for their disease-modifying effect, especially in early RA. When used in a dosage of 7.5–10 mg/day, most adverse effects can be handled quite well, although monitoring for and awareness of infections are important. Adverse events may have been overreported, due to bias by indication, but pose an important drawback in the use of these very effective anti-inflammatory and immune-modulatory drugs. Daily dosages >7.5–10 mg and use for a prolonged period (years) of time are associated with a dose-dependent increased mortality. Still, the benefit:risk ratio for low-dosage glucocorticoid in patients with RA is acceptable and in many ways is comparable with other synthetic and biologic DMARDs.

Key words: glucocorticoids, adverse events, rheumatoid arthritis, cardiovascular disease, infections

Rheumatology key messages

- Adverse events in glucocorticoid treatment could be overreported due to bias by indication.
- Adverse events in glucocorticoid treatment pose an important disadvantage in the use of anti-inflammatory and immune-modulatory drugs.
- The benefit:risk ratio for low-dose glucocorticoids in RA patients is acceptable and comparable to synthetic and biologic DMARDs.

Introduction

The first time glucocorticoids (GCs) were used in a patient with RA there was an impressive effect: the bedridden patient started to walk again. This miracle led to extremes of exaggerated praise, but soon thereafter to bitter denunciation and emotion-laden criticisms based on observed adverse events (AEs) during indiscriminate use of high dosages of GCs. Although some of the emotions around the use of GCs have now been tempered, finding the right balance between the advantages and disadvantages is still a matter of ongoing debate [1]. Recent information from European databases indicates that about half of all RA patients are using concomitant GC therapy for a more prolonged period of time, nearly all in dosages <7.5 mg of prednisone equivalent/day. It is well accepted that the balance between efficacy and AEs at and below this dosage can be considered favourable [2].

In Table 1, the summed reported AEs from 18 studies among patients using GCs for a rheumatic disease are presented, showing a very wide range of reported AEs [3]. This is the reason for the many different opinions of rheumatologists on the safety of GCs. These AEs of low-dose GCs are well known but need to be evaluated in the context of the treated inflammatory condition. Chronic inflammation increases the risks of cardiovascular (CV) diseases, infections, insulin resistance, inflammatory bone loss and other co-morbidities. Reducing these risks by reducing chronic inflammation may in some way counterbalance the negative effects of GCs; GCs can therefore be considered as a double-edged sword [4].

Crucial in the long-term treatment of RA is, ultimately, survival. Epidemiological data suggest that RA has a negative effect on survival; in the past this was estimated at 10 years less life expectancy and more recently it has been estimated at 5–7 years less life expectancy [5, 6]. Factors attributing to early mortality include poor

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TABLE 1 Reported AEs in 18 studies among 963 patients using GCs for a rheumatic disease

Adverse event	Median (25th–75th percentiles) AEs per 100 patient-years
Cardiovascular	15 (3–28)
Infectious	15 (3–15)
Gastrointestinal	10 (4–20)
Psychological/behavioural	9 (2–36)
Endocrine/metabolic	7 (3–34)
Dermatological	5 (2–80)
Musculoskeletal	4 (3–9)
Ophthalmological	4 (0–5)

Adapted from Hoes *et al.* [3], with permission from BMJ Publishing Group. Data show a wide range of AEs across 18 studies with 963 patients.

functional capacity, co-morbidities and markers of disease severity or activity. It has been suggested that the use of some drugs, including GCs, may play a role in this increase in mortality. On the other hand, successful control of disease activity (by treatment with MTX) has been reported to reduce mortality in RA [7]. Two recent studies evaluated mortality in RA and the possible relationship with the use of GCs—one in the German biologics register RA oBservation of Biologic Therapy and the other in an observational cohort study in Texas, USA.

Registry data

Data from the RA oBservation of Biologic Therapy registry, based on an ongoing prospective cohort study that started in 2001, were evaluated. RA patients who had failed at least one synthetic DMARD and thereafter started with a second synthetic or a first biologic DMARD were included: 2060 on MTX, 928 on another synthetic DMARD, 4649 on TNF-α inhibitors, 703 on rituximab and 568 on another biologic (N = 8909) [8]. During >31 000 patient-years of follow-up, 463 of the 8909 patients died, giving a reported standardized mortality ratio of 1.49 (95% CI 1.36, 1.63). The authors set out to estimate the association between persistent highly active disease and mortality and to evaluate the mortality risk of patients treated with biologic DMARDs *vs* synthetic DMARDs. Primary analyses were based on multiple Cox regression analysis with pre-specified fixed and time-dependent risk factors. Fixed risk factors (at baseline) included age, sex, smoking and comorbid conditions. Time-dependent risk factors (each time of evaluation) included the 28-joint DAS (DAS28) and treatment with GCs, other synthetic DMARDs and biologic DMARDs. Patients with persistent highly active disease (mean DAS28 >5.1) had a significantly higher mortality risk [adjusted hazard ratio (HR) = 2.43 (95% CI 1.64, 3.61)] than patients with persistent low disease activity (mean DAS28 <3.2). Treatment with >5 mg/day GC during the most recent 12 months was significantly associated with increased mortality, independent of disease activity: 1–5 mg GC adjusted HR = 1.05 (95% CI 0.80, 1.38); 6–10 mg adjusted HR = 1.46 (1.09, 1.95); 11–15 mg adjusted HR = 2.00 (1.29, 3.11) and >15 mg adjusted HR = 3.59 (2.11, 6.13). Significantly lower mortality was observed in patients treated with TNF-α inhibitors [adjusted HR = 0.64 (95% CI 0.50, 0.81)], rituximab [adjusted HR = 0.57 (95% CI 0.39, 0.84)] and other biologics [adjusted HR = 0.64 (95% CI 0.42, 0.99)] compared with MTX. As expected, higher mortality was observed in RA patients with co-morbid conditions, such as diabetes, chronic lung or renal disease or coronary heart disease; no details on the specific mortality causes were given.

The analysis with regard to the association between GC use and mortality warrants some comments. In general, the use of GCs can be considered an indicator for more severe disease, and this observed association may reflect the persistently high disease activity at the moment GCs were prescribed. The adjusted HRs were calculated with the DAS28 (and others) at the actual moment of inclusion in the registry, when the presumed beneficial effect of the previously started GC on disease activity had already influenced the DAS. Therefore, bias by indication may still play a role in this analysis, as also stated by the authors in their discussion of these data. As we have explained before, the only way to completely rule out this bias by indication is by randomizing patients to GC or placebo in well-conducted clinical trials. The AE rates in these randomized controlled trials, which are of course limited in duration, are often equal to and sometimes even lower than in the comparator groups with placebo, for example, in the Computer-Assisted Management in Early RA II study [9].

Observational cohort study

Between January 1996 and April 2001, 779 RA patients were consecutively recruited from six Texas rheumatology clinics; a thorough baseline evaluation and subsequent annual follow-up assessments were performed [10]. As well as demographic, socio-economic, clinical and laboratory features, data on GC use and dosage, CV risk factors and vital signs were collected. At baseline, 386 patients did not use GCs, while 393 used GCs, with a mean daily dosage of 6.9 mg/day and a cumulative dosage of 12.5 g (S.D. 16.4). There were no significant differences between these two groups, although disease duration was slightly longer (12 *vs* 10 years) and disease activity slightly higher in the GC users. At evaluation there were 7203 patient-years of observation and 237 patients had died. Patients that received GCs during the observation period experienced 142 deaths [mortality rate 4.3/100 patient-years (95% CI 3.6, 5.0)]; patients who did not receive GCs during the pooled follow-up period experienced 95 deaths [mortality rate 2.4/100 patient-years (95% CI 1.9, 2.9)]. There were 120 deaths from CV causes: 72 in GC-exposed patients [2.5/100 patient-years (95% CI 1.9, 3.1)] and 48 in the non-exposed patients [1.3/100 patient-years (95% CI 0.9, 1.7)]. Death from all causes and death from CV causes, adjusted for covariates (in four different Cox proportional hazards models,

starting with GC dosage, then adding demographic and socio-economic variables, then adding clinical and laboratory manifestations of RA and as a last step adding CV risk factors), were quantitatively associated with GC exposure. The adjusted HR for all-cause mortality was 1.78 (95% CI 1.22, 2.60) for a daily dosage of 8–15 mg and 2.83 (95% CI 1.41, 5.66) for >15 mg; for dosages below 8 mg/day the 95% CI included 1.00: < 5 mg/day 1.19 (95%CI 0.74-1.90), 5-7mg 1.21 (95%CI 0.88-1.66). The same pattern was seen for CV death. Thus at the lowest daily exposure levels, death rates were not significantly different from those among patients who had not been exposed to GCs, but in progressively higher dose strata the risk of death increased. This dose response was apparent for both daily and cumulative exposures. The authors conclude that daily prednisone doses ⩽7.5 mg in RA patients may be safe from the standpoint of mortality risk, but higher dosages are not. Similarly, a cumulative prednisone dose <40 g (nearly 15 years at 7.5 mg/day) was associated with a mortality risk that was no different from that in unexposed patients. Again, above this threshold mortality rates increased. Of course, these data cannot be extrapolated to an individual patient's risk, but nevertheless may help clinicians in selecting the appropriate GC dosage for their patients, weighing benefits and risks.

Discussion

These reported studies give some insights into real-life data about AEs during the use of GCs in patients with RA, with a focus on CV events and mortality. They underscore the necessity of prudent use of GCs, very powerful drugs that can improve the quality of life of many RA patients. In line with these findings, the recent EULAR recommendations on the use of medium to high dosages of GCs in rheumatic disease [11] are mentioned below.

Before starting GC treatment, consider co-morbidities predisposing to AEs. These include diabetes, glucose intolerance, CV disease, chronic infections, severe immunosuppression and risk factors for glaucoma and osteoporosis. Patients with these co-morbidities require especially tight control of their dosages to manage the risk:benefit ratio. Select the starting dose as the (expected) minimum required to achieve therapeutic response.

The requirement for continuing GC treatment should be constantly reviewed and the dose should be titrated against the therapeutic response and development of adverse effects.

All patients should have regular monitoring for frequent, clinically significant adverse effects. The minimum set of items to monitor includes diabetes, hypertension, lipids, weight gain, oedema, osteoporosis (hidden), infections, osteonecrosis, myopathy, eye problems, skin problems and neuropsychological effects.

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